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Catalytic Enantioselective Cyclization/Cross-Coupling with Alkyl Electrophiles

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Supporting Information

ABSTRACT: As part of our ongoing effort to expand the scope of cross-coupling reactions of alkyl electrophiles, we have pursued a strategy wherein the nucleophilic coupling partner includes a pendant olefin; after transmetalation by such a substrate, if β-migratory insertion proceeds faster than direct cross-coupling, an additional carbon−carbon bond and stereocenter can be formed. With the aid of a nickel/diamine catalyst (both components are commercially available), we have established the viability of this approach for the catalytic asymmetric synthesis of 2,3-dihydrobenzofurans and indanes. Furthermore, we have applied this new method to the construction of the dihydrobenzofuran core of fasiglifam, as well as to a cross-coupling with a racemic alkyl electrophile; in the latter process, the chiral catalyst controls two stereocenters, one that is newly generated in a β-migratory insertion and one that begins as a mixture of enantiomers.

In recent years, significant progress has been reported on the development of methods for the transition-metal-catalyzed cross-coupling of alkyl electrophiles to generate carbon−carbon bonds, including enantioselective processes.[1] To date, most investigations of asymmetric catalysis have focused on stereoconvergent reactions of racemic secondary electrophiles,[2] although an advance has also been described with a racemic secondary nucleophile (top of Figure 1).[3]

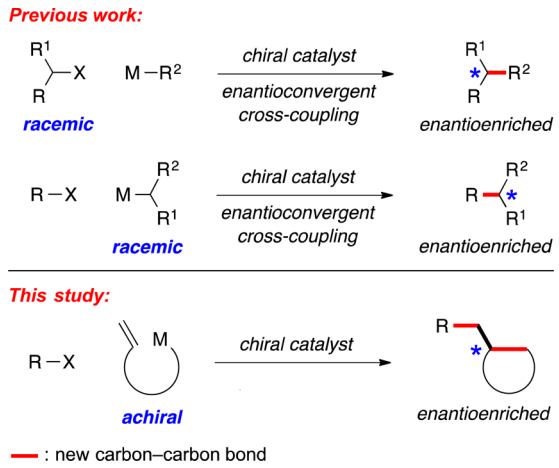

Figure 1. Asymmetric cross-couplings of alkyl electrophiles.

As part of our ongoing effort to expand the scope of enantioselective cross-couplings of alkyl electrophiles, we are pursuing an approach wherein an organometallic reagent that bears a pendant olefin is employed as the nucleophilic coupling partner (bottom of Figure 1).[4−6] In the presence of a chiral catalyst, transmetalation and then β-migratory insertion (left side of Figure 2), followed by alkyl−alkyl coupling, could lead

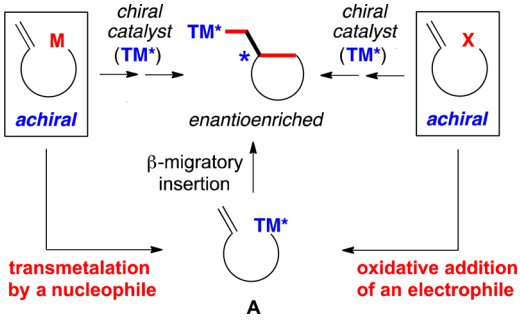

Figure 2. Complementary approaches to generating a precursor (A) for catalytic enantioselective cyclizations.

to the formation of two carbon−carbon bonds and a new stereocenter (bottom of Figure 1). This strategy complements asymmetric coupling processes wherein an intermediate of type **A** is generated through oxidative addition of an electrophile (right side of Figure 2).[7]

In this report, we establish that a transmetalation−insertion sequence can indeed be used to generate two, rather than one, carbon−carbon bonds in a cross-coupling with an alkyl electrophile and that this process can be achieved with good enantioselectivity. Specifically, we describe couplings of arylboron reagents that bear a pendant olefin with unactivated alkyl halides, thereby furnishing 2,3-dihydrobenzofurans[8,9] and indanes[10,11] in high ee (eq 1).

In order to enhance the likelihood of cyclization (β-migratory insertion) prior to coupling with the electrophile, we chose to focus on an organometallic coupling partner that could form a five-membered ring upon insertion, since such cyclizations are often facile. At the outset, it was unclear what catalyst would enable the desired sequence of bond-forming processes, much less achieve high enantioselectivity.

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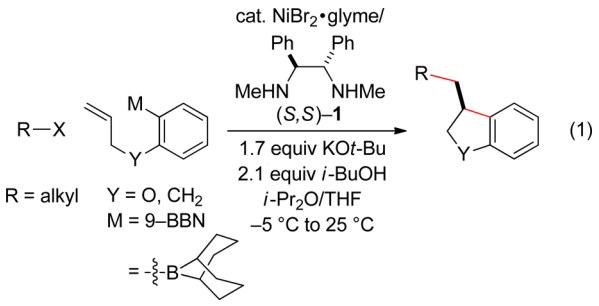
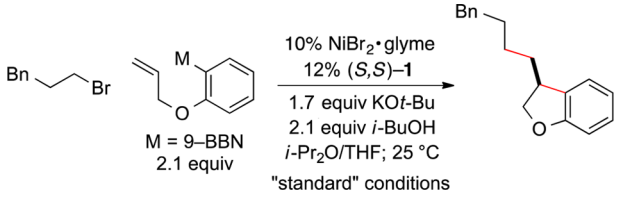
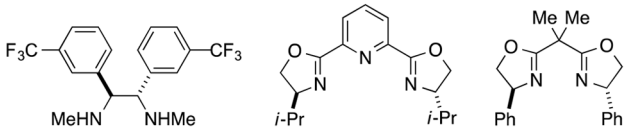


Interestingly, we have determined that a nickel/1,2-diamine-based catalyst, which we have found to be useful for enantioconvergent alkyl–alkyl couplings,[3,12] is also effective for the desired cyclization/cross-coupling sequence (Table 1, entry 1). Thus, in the presence of $NiBr_2$·glyme and ligand **1**, both of which are commercially available, the target 2,3-dihydrobenzofuran is generated in good ee and yield. Under these conditions, essentially none of the product of direct cross-coupling (without cyclization of the nucleophile) or of endo cyclization is observed (<5%).

Table 1. Catalytic Enantioselective Cyclization/Cross-Coupling with an Alkyl Electrophile: Influence of Reaction Parameters[a]



entry	variation from the "standard" conditions	ee (%)	yield (%)[b]
1	none	96	82
2	no $NiBr_2$•glyme	–	<5
3	no (*S*,*S*)–**1**	–	<5
4	no *i*-BuOH	–	<5
5	1.5 equiv of arylboron reagent	81	67
6	(*S*,*S*)–**2**, instead of (*S*,*S*)–**1**	39	64
7	(*S*,*S*)–**3**, instead of (*S*,*S*)–**1**	–	<5
8	(*S*,*S*)–**4**, instead of (*S*,*S*)–**1**	61	33
9	$BnCH_2CH_2Cl$, instead of $BnCH_2CH_2Br$	–	<5

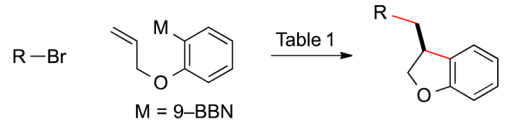


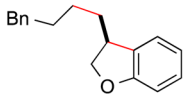
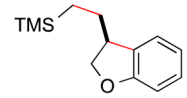
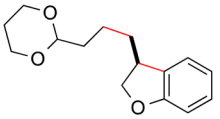
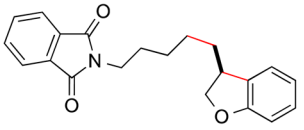
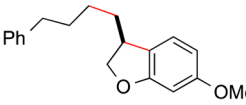
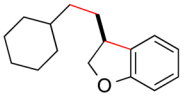
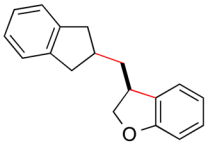
[a]All data are the average of two experiments. [b]The yield was determined by GC analysis with the aid of a calibrated internal standard.

In the absence of $NiBr_2$·glyme, ligand **1**, or *i*-BuOH, the desired cyclization/cross-coupling product did not form in appreciable yield (Table 1, entries 2–4).[13] Furthermore, the use of a smaller excess of the arylboron reagent led to a somewhat lower ee and yield (entry 5).[14] Other ligands that we have found to be useful for enantioconvergent couplings of alkyl electrophiles were not effective for this new asymmetric cross-coupling with an alkyl halide (entries 6–8).[15] If the alkyl bromide was replaced with the corresponding alkyl chloride, essentially no 2,3-dihydrobenzofuran was observed (entry 9).[16]

We next examined the scope of this method for asymmetric cyclization/cross-coupling with alkyl bromides (Table 2).[17] A range of functionalized electrophiles serve as suitable reaction partners, furnishing the desired 2,3-dihydrobenzofuran in very good enantiomeric excess. A silane, an acetal, and an imide are compatible with the reaction conditions. The method is not limited to unhindered primary alkyl bromides; a β-branched primary and a secondary bromide also undergo cyclization/cross-coupling (entries 6 and 7).

Table 2. Catalytic Enantioselective Cyclization/Cross-Coupling with Alkyl Electrophiles[a]



entry	product	ee (%)	yield (%)[b]
1		95	77
2		96	47
3		97	69
4		97	67
5		94	45[c]
6		96	58
7		96	52

[a]All data are the average of two experiments. [b]Yield of purified product. [c]15% $NiBr_2$·glyme and 17% ligand **1** were used.

Under similar conditions, indane derivatives can also be produced in high ee, although modest yield (eq 2).[17c] An attempt to generate a quaternary stereocenter furnished a promising initial result (eq 3).

A number of optically active 2,3-dihydrobenzofurans exhibit interesting biological activity,[8,9] including fasiglifam (Takeda Pharmaceuticals: TAK-875), which progressed to phase 3 clinical trials for type 2 diabetes until being withdrawn due to concerns about liver safety.[18] We have applied our method to a catalytic asymmetric synthesis of the dihydrobenzofuran core of fasiglifam (Scheme 1).

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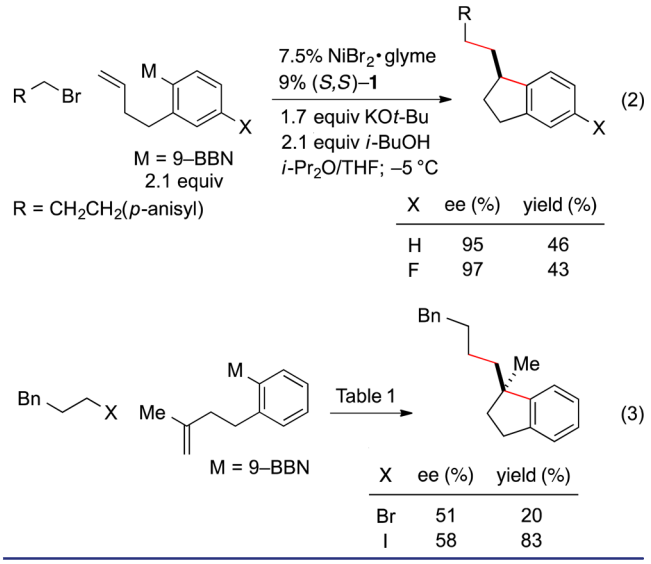
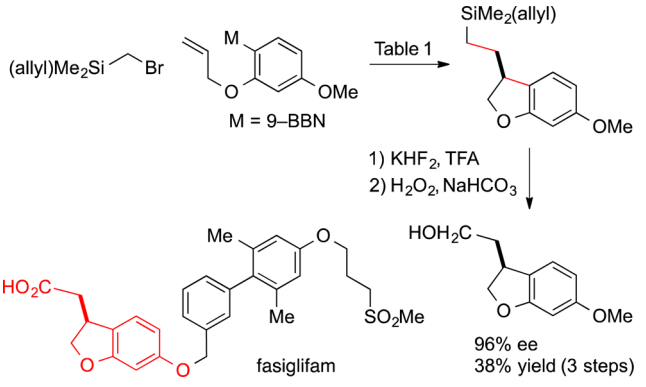
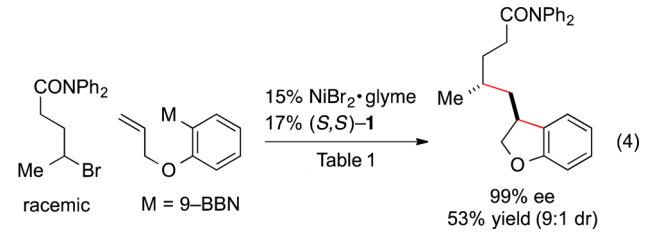


Scheme 1. Catalytic Asymmetric Synthesis of the 2,3-Dihydrobenzofuran Core of Fasiglifam



In view of the similarity of the optimized conditions for this new asymmetric cyclization/cross-coupling process to those for our stereoconvergent cross-coupling of racemic γ-haloamides,[12d] we investigated the possibility that a single chiral catalyst could accomplish two distinct enantioselective transformations: create a new stereocenter through the cyclization of an achiral nucleophile, as well as control the absolute stereochemistry of a second stereocenter through an enantioconvergent coupling of a racemic electrophile. As illustrated in eq 4, this objective can indeed be achieved (minor diastereomer: 86% ee).



In summary, we have expanded the scope of cross-coupling reactions of alkyl electrophiles by incorporating an olefin in the nucleophilic partner, which leads to the formation of an additional carbon–carbon bond and stereocenter, when compared with a simple cross-coupling. With the aid of a nickel/diamine catalyst (both components are commercially available), we have established that this strategy enables the synthesis of highly enantioenriched 2,3-dihydrobenzofurans and indanes through couplings with a range of alkyl halides. We have applied this new method to the generation of the dihydrobenzofuran core of fasiglifam, as well as to a transformation wherein the chiral catalyst controls the stereochemistry of two rather different processes: a β-migratory insertion and an enantioconvergent coupling of a racemic alkyl halide. Ongoing studies are directed at further enlarging the scope of cross-coupling reactions of alkyl electrophiles, as well as elucidating the mechanisms of these transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Codeine is an example of a bioactive compound that includes a 2,3-dihydrobenzofuran.
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(11) Rasagiline, which is used for the treatment of Parkinson's disease, is an example of a simple bioactive compound that includes an indane: Hoy, S. M.; Keating, G. M. *Drugs* **2012**, *72*, 643−669.
(12) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694−6695. (b) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908−11909. (c) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154−8157. (d) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362−15364. (e) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794−5797.
(13) The failure to observe a significant amount of the cross-coupling product in the absence of *i*-BuOH (entry 4 of Table 1) could be due to less effective transmetalation in the absence of a less bulky alkoxide.
(14) Some of the nucleophile is consumed in the reduction of the Ni(II) precatalyst to the active catalyst. A small amount also undergoes protodeborylation under the reaction conditions.
(15) For example, see: (a) Pybox ligand: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595. (b) Bis(oxazoline) ligand: Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264−1266.
(16) The alkyl chloride is largely intact at the end of the reaction (>95%).
(17) Notes: Under our standard conditions (Table 1): (a) The coupling illustrated in Table 2, entry 1 proceeded in 96% ee and 67% yield on a gram scale (1.07 g of product). (b) An initial attempt to form a six-membered ring through cyclization/cross-coupling of a homologated arylboron reagent was not successful. (c) In general, the primary undesired side reactions are reduction (hydrodehalogenation) and electrophile homocoupling. (d) PhBr is not a suitable electrophile. (e) An indoline can be generated with promising enantioselectivity and yield (54% ee, 40% yield).
(18) For a discussion and leading references, see: (a) Takeda web page. http://www.takeda.com/news/2013/20131227_6117.html (accessed January 18, 2014). (b) Negoro, N.; Sasaki, S.; Mikami, S.; Ito, M.; Suzuki, M.; Tsujihata, Y.; Ito, R.; Harada, A.; Takeuchi, K.; Suzuki, N.; Miyazaki, J.; Santou, T.; Odani, T.; Kanzaki, N.; Funami, M.; Tanaka, T.; Kogame, A.; Matsunaga, S.; Yasuma, T.; Momose, Y. *ACS Med. Chem. Lett.* **2010**, *1*, 290−294. (c) Kaku, K. *Expert Opinion on Pharmacotherapy* **2013**, *14*, 2591−2600. (d) de Lartigue, J. *Drugs of the Future* **2011**, *36*, 813−818.